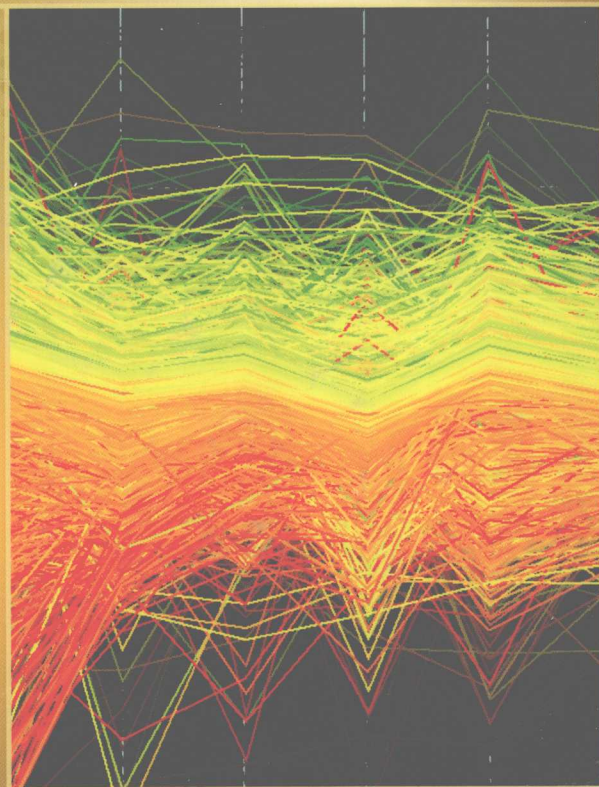


Handbook of Systems Toxicology

Editors Daniel A. Casciano and Saura C. Sahu



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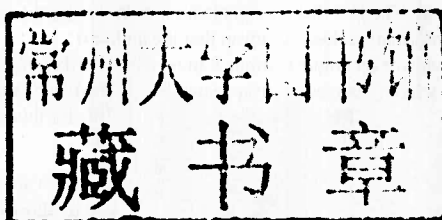
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Preface

One result of the sequencing of the human genome has been the development of a variety of new and emerging technologies which allow the researcher to determine how a cell, tissue, organ or organism functions at the molecular level. These technologies include genomics, proteomics, metabolomics and bioinformatics. A consequence of this development is the initiation of a systems biology approach to understanding the normal or constitutive function of an organism. Systems biology focuses on understanding gene and protein networks involved in cell signaling communication between cells and cellular metabolic pathways. This new approach requires an integration of several scientific disciplines using talents from multidisciplinary research teams. Systems toxicology, a natural derivative of systems biology, combines classical toxicology with the rapidly developing new “omics” technology providing integrated biological response data that describe molecular pathways that are perturbed by a toxicant much sooner than a toxin-induced phenotype is observed, allowing definition of predictive biomarkers. It integrates molecular expression data sets from transcriptomics, proteomics, metabolomics and conventional toxicology with metabolism, toxicological pathways and gene regulatory network information relevant to human toxicology and disease. Systems toxicology develops new primary data as well as an assessment of available data to understand how the molecular machinery of biological systems execute their biological functions in the presence of chemical and biological stress.

Humans are exposed to many chemicals every day in the modern industrial world and the evaluation of the risk of these chemicals to human health requires a better understanding of the mechanism(s) of their toxicity. In the last decade the emergence of the new “omics” technologies has generated a vast amount of molecular information on the effects of chemical toxicants in biological systems such as cells, tissues,

organs and organisms. As the emerging technologies mature, the National Academy of Sciences Committee on Toxicity Testing and Assessment of Environmental Agents recommended, in 2007, a new approach to toxicity testing embracing the use of these new tools. Advances in systems toxicology will help develop new strategies for mechanistic and predictive toxicology resulting in new predictive biomarkers using a combination of cross-“omics” and classical toxicology endpoints to detect toxicants much earlier in the toxicity process. Another outcome is the identification of more sensitive and predictive biomarkers of toxicity that will aid in the development and approval of safer and more effective drugs, foods and medical devices. Also, the derived data will facilitate the development of better models of species extrapolation allowing a more relevant assessment of human risk. Development and validation of this emerging science should provide toxicologists with greater confidence using the data developed in our present animal models and should ensure the development of newer models that are more mechanistically relevant in their application to human risk assessment. Additionally, these tools can be used to directly assess human toxicity resulting in more accurate animal and mathematical models for the identification of risk to humans.

Prior to assembling this treatise, we found little or no integrated literature describing this new area of toxicology. The main purpose of this handbook then was to assemble up-to-date, state-of-the-art information presented by investigators who are internationally recognized in their particular research areas. It is therefore hoped that the work will become an authoritative source of current knowledge in this particular area of research. The book is designed primarily for the research scientist currently engaged in this field. However, it should be of interest to scientists in a wider set of disciplines

including toxicology, genetics, medicine and pharmacology as well as drug and food sciences. Also, it should be of interest to federal regulators and risk assessors of drugs and foods, and of environment and consumer products. We have included a section on nanotechnology and nanotoxicology because it is a new area of discovery directed to human use that may have a significant impact on how these materials are used and regulated. We feel that the application of tools resulting from a systems toxicology approach to nanoparticles will provide us with a greater level of confidence in their human efficacy and toxicity.

Since the field of systems toxicology is a rapidly developing, emerging branch of modern toxicology it is expected that there will be a requirement for regular updates to this volume. Although the fundamental concepts presented in these volumes are unchanging, the emergence of new experimental models and new bioinformatic tools will dictate regular updating to track the maturation and validation of this extremely exciting area of toxicology.

Daniel A. Casciano

Saura C. Sahu

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Abbreviations and Acronyms

1O2	Singlet Oxygen	ADMET	Adsorption Distribution, Metabolism, Excretion and Toxicity
2-AG	2-Arachidonoylglycerol		
2D-DIGE	2D Difference In Gel Electrophoresis	AERS	Adverse-Event-Reporting System
2-DE	Two-Dimensional Electrophoresis	AEs	Adverse Events
2D-PAGE	Two-Dimensional Polyacrylamide Gel Electrophoresis	AF	Attributable Fraction
		AFM	Atomic Force Microscopy
2-OG	2-Oxoglutarate	AHPS	American Herbal Products Association
3-NP	3-Nitropropionic Acid	AhR	Aryl Hydrocarbon Receptors
4-NQO	4-Nitroquinoline 1-Oxide	AIR	Acute Inflammatory Response
5-FU	5-Fluorouracil		
8-OHdG	8-Hydroxydeoxyguanosine	ALA	Amino Levulinic Acid
8-OHG	8-Hydroxyguanosine	ALAT	Alanine Aminotransferase
AA	Arachidonic Acid	ALD	Alcohol Liver Disease
AA	Aristolochic Acid	ALF	Artificial Lysosomal Fluid
ABC	Ammonium Bicarbonate	ALL	Acute Lymphoblastic Leukemia
ABH6	$\alpha\beta$ -Hydrolases 6		
Abhd6	Abhydrolase Domain Containing 6	ALP	Alkaline Phosphatase
ABM	Agent-Based Modeling	ALT	Alanine Aminotransferase
ACAT	Advanced Compartmental Absorption and Transit	ALT	Alanine
			Aminotransaminase
ACD	Available Chemical Database	AM	Acetoxymethyl
ACD	Available Chemical Directory	AM	Alveolar Macrophages
		AML	Acute Myeloid Leukemia
ACToR	Aggregated Toxicology Resource	AMPA	α -Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionate Receptors
AdFAAH	An Faah-Expressing Adenovirus		
AdGFP	GFP-Expressing Control Virus	AMs	Alveolar Macrophages
ADME	Absorption, Distribution, Metabolism, and Elimination	AMT	Accurate Mass and Time Tags
		AMV	Avian Myeloblastoma Virus
		ANIT	1-Naphthylisothiocyanate
		ANOVA	Analysis of Variance

AP	Action Potential	C/EBP	Ccaat/Enhancer-Binding Protein
Apaf-1	Apoptotic Protease	CA	Chromosomal Aberration
APAP	Activating Factor-1	CADD	Computer Assisted Drug Design
N-APAP	Acetaminophen	CAM	Caulis Aristolochiae
APASE	N-Acetyl-P-Aminophenol	CAMD	Manshuriensis
APD	Alkaline Phosphatase	CAPs	Computer-Assisted Molecular Design
AR	Action Potential Duration	CASP	Common Ageing Profiles
AR	Aldose Reductase	CAVE	Critical Assessment of Structure Prediction
AR	Aldose Reductase	CB	Cave Automatic Virtual Environment
ARE	Androgen Receptor	CB	Cannabinoid
ARE	Antioxidant Response Elements	CBD	Carbon Black
ARF	Acute Renal Failure	CBPR	Cannabidiol
ARS	Agricultural Research Service	CCAT	Community-Based Participatory Research
ASAT	Aspartate	CCl ₄	Chemically-Coded Affinity Tag
ATHEROMA	Aminotransferase	CDC	Carbon Tetrachloride
	Atorvastatin Therapy: Effects on Reduction of Macrophage Activity	CDER	Center for Disease Control and Research
ATZ	Atrazine	CDKs	Center for Drug Evaluation and Research
AUC	Area Under the Curve	CEBS	Cyclin-Dependent Kinases
AV	Atrioventricular	CeO ₂	Chemical Effects in Biological Systems
AXL	Axial	CFD	Cerium Oxide
BAL	Bronchoalveolar Lavage	CFF	Computational Fluid Dynamics
BaP	Benzo[A]Pyrene	CFSAN	Consistent Force Field
BBB	Blood-Brain Barrier	CG	Center for Food Safety and Nutrition
BBDR	Biologically Based Dose-Response	CGAs	Comparative Genometrics
BDL	Bile Duct Ligation	CHCA	Community Genome Arrays
BDPE	Benzo[A]Pyrene Diol Epoxide	CHI	α -Cyano-4-Hydroxycinnamic Acid
BDSM	Birth Defects Systems Manager	CHIC	Closed Head Injury
BE	Binding Energy	ChIP	Community Health Improvement
BEAS-2B	Bronchial Epithelial Cells	CID	Collaborative Chromatin Immunoprecipitation
BED	Biologically Effective Dose	CIM	Collision-Induced Dissociation
BET	Brunauer, Emmett, and Teller	CIM	Cimetidine
BMD	Benchmark Dose	CL	Chemiluminescent
BOINC	Berkeley Open Infrastructure for Network Computing	cLEL	Categorical Lels
BOSS	Biochemical and Organic Simulation System	CLH	Hepatic Clearance
BSI	British Standards Institution		
B-TOH	Bopidy- α -Tocopherol		
BUN	Blood Urea Nitrogen		
BW	Body Weight		